REMARKS/ARGUMENTS

Claims 1 and 30 remain in the application. Reconsideration of this application, in view of these remarks, is respectfully requested.

Claims 1 and 30 stand rejected under 35 U. S. C. §103(a) as being unpatentable over Schwartz (U. S. 2003/0013857 A1). This rejection is respectfully traversed for the following reasons.

Schwartz, U.S. Patent Application Publication 2003/0013857 A1 (hereinafter "Schwartz"), discloses modified solid supports that include solid supports that have been modified by reaction with a bifunctional reagent that possess a hydrazine or oxyamino group. These modified solid supports are useful in immobilization of biomolecules that possess or are modified to possess a carbonyl group. In one embodiment, aliphatic bifunctional hydrazide reagents are provided. See paragraph [0018] of Schwartz. These reagents include a cleavable bond for further manipulation. Cleavable bonds include, but are not limited to, acid cleavable, photocleavable and disulfide bonds. See paragraph [0109] in Schwartz.

Schwartz discloses a method of attaching a protein to a functionalized solid surface through a hydrazone linkage. The protein is immobilized to a functionalized solid support via hydrazone bond formation. Schwartz discloses hydrazone bond formation as useful for conjugating biomolecules to other biomolecules and to fluorescent dyes. Schwartz discloses cleavage of the hydrazone bond to form useful products. However, Schwartz does not describe the preparation of conjugates comprising two macromolecules using conventional bifunctional reagents.

None of the conjugates described in Examples 12, 14, 16, 20 of Schwartz correspond to the conjugates of the present invention, which comprise a First Macromolecule and at least one Second Macromolecule, because the conjugates described in Schwartz include a hydrazone bond linking the First Macromolecule and the Second Macromolecule. The hydrazone bond has been described as being cleavable, both by Schwartz and the specification of the present application. It is clear from paragraphs [0057] and [0110] of the specification of the present application that the linker between the First Macromolecule and the solid is cleavable. The specification of the present application does not specifically state that the linker between the First Macromolecule and the at least one Second

Macromolecule is not cleavable. Although claims 1 and 30 do not recite that the linker between the First Macromolecule and the Second Macromolecule is not cleavable, it is clear that the methods recited in claims 1 and 30 do not result in cleavage of the linker between the First Macromolecule and the Second Macromolecule. The reason for this important conclusion is that the conjugate, which is the ultimate product that is recovered from the methods recited in claims 1 and 30, could not exist after the complex comprising the First Macromolecule and the Second Macromolecule is detached from the solid support, unless the linker joining the First Macromolecule and the Second macromolecule were unable to be cleaved in the methods claimed. Thus, it is clear that Schwartz teaches away from the methods recited in claims 1 and 30, because Schwartz calls for the cleavage of the First Macromolecule (protein) from the Second macromolecule (protein), which cleavage would result in the destruction of the conjugate. In view of the foregoing, it is submitted that Schwartz does not render claims 1 and 30, as amended, obvious to one of ordinary skill in the art.

Upon a more detailed review of Schwartz, it is clear that Schwartz does disclose methods for attaching a first macromolecule to a second macromolecule. See for example, paragraphs [0110], [0111], and [0112] of Schwartz. Paragraph [0110] of Schwartz describes the use of cleavable linkers to create a drug-antibody conjugate, which is cleaved by physiological processes following endocytosis. Schwartz also refers to the use of cleavable disulfide linkages to isolate receptors following covalent linking between a ligand and a receptor. This paragraph of Schwartz fails to disclose or suggest a method of preparing a conjugate in which a First Macromolecule of the conjugate is not cleaved from a Second Macromolecule of the conjugate. Paragraph [0111] of Schwartz describes the use of bifunctional hydrazides to modify biomolecules or carriers in a single step. These modified aliphatic hydrazide molecules or carriers can be subsequently reacted with carbonyl containing biomolecules, drug, or other therapeutic or diagnostic reagent to form a hydrazone that can be cleaved following exposure to mild aqueous acid conditions. Like paragraph [0110] of Schwartz, this paragraph of Schwartz fails to disclose or suggest a method of preparing a conjugate in which a First Macromolecule of the conjugate is not cleaved from a Second Macromolecule of the conjugate. Paragraph [0112] of Schwartz describes that solid supports such as

beads, chromatographic supports or surfaces are modified with aliphatic hydrazide reagents. Like paragraphs [0110] and [0111] of Schwartz, this paragraph of Schwartz fails to disclose or suggest a method of preparing a conjugate in which a First Macromolecule of the conjugate is not cleaved from a Second Macromolecule of the conjugate. Thus, it is clear that Schwartz fails to disclose or suggest a method that would provide a conjugate having the stability possessed by the conjugates recited in claims 1 and 30.

It is clear that Schwartz also describes methods for attaching a chain of macromolecules to a surface. See, for example, paragraphs [0147], [0150], [0158], [0177], [0179], and EXAMPLES 6, 7, 8, 18, and 21 of Schwartz.

(a) Paragraph [0147] of Schwartz describes hydrazino modified beads for forming stable hydrazones when reacted with molecules possessing carbonyl groups.

(b) Paragraph [0150] of Schwartz describes hydrazine and oxyamino silanes that are useful for modification of silica surfaces to generate hydrazine and oxyamino glass.

(c) Paragraph [0158] of Schwartz describes reagents to incorporate hydrazine and oxyamino groups on thiophilic metals, surfaces and particles.

(d) Paragraph [0177] of Schwartz describes that the reagent provided therein may be utilized to form crosslinks between a wide variety of molecules, including. for example, protein-protein conjugates (e.g., monoclonal antibody/enzyme conjugate) or protein-polymer conjugates (e.g., monoclonal antibody to a microtiter well surface).

(e) Paragraph [0179] of Schwartz describes immobilization of biomolecules to surfaces using a crosslinking couple by modifying the biomolecule with either a hydrazino, oxyamino, or a carbonyl moiety and contacting the modified biomolecule to a surface possessing its reactive partner, e.g., a hydrazino or oxyamino moiety for a carbonyl-modified biomolecule, or a carbonyl moiety for a hydrazino- or oxyamino-modified biomolecule.

(f) EXAMPLE 6 of Schwartz describes modification of glass surfaces by

hydrazone-protected hydrazine silane reagent.

(g) EXAMPLE 7 of Schwartz describes prepration of 96 well plates to incorporate aromatic aldehyde moieties.

(h) EXAMPLE 8 of Schwartz describes preparation of 96 well plates to incorporate aromatic hydrazine moieties.

(i) EXAMPLE 18 of Schwartz describes a general procedure for the modification of gold particles with succinimidyl hydrazinium modification reagent.

(j) EXAMPLE 21 of Schwartz describes immobilization of horseradish peroxidase to hydrazine-modified plates.

However, Schwartz fails to disclose or suggest a method having a plurality of steps, wherein all of the following steps are included:

(1) linking a First Macromolecules to a surface,

(2) linking at least one Second Macromolecule to the First Macromolecule, and

(3) disrupting the link between the First Macromolecule and the surface in order to free the conjugate comprising the First Macromolecule and the at least one Second Macromolecule from the surface without disrupting the covalent bond existing between the First Macromolecule and the at least one Second Macromolecule.

Accordingly, Schwartz does not disclose or suggest a method containing all of the steps of the method described and claimed in this application.

Although Schwartz provides a number of descriptions of conjugations between biomolecules and solid supports and although Schwartz also provides a number of descriptions of cleavable linkers, Schwartz does not disclose or suggest a method for carrying out the methods described in claims 1 and 30.

In view of the foregoing, it is submitted that claims 1 and 30, as amended, are in condition for allowance, and official Notice of Allowance is respectfully requested.

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